Atty's Docket:101195-38

CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, Applicants request that this be considered a petition therefore. Please charge the required fee to Deposit Account No. 14-1263.

ADDITIONAL FEES

Please charge any further insufficiency of fees, or credit any excess to Deposit Account No. 14-1263.

REMARKS

Claims 15-26 are pending. All claims have been rejected.

Claim 15 has been amended.

New claim 27 has been added. The claim is directed to the transferring of genetic material being performed *in vivo*. Persons of skill in the art would readily appreciate from the specification that the in vivo embodiment of the method is encompassed therein. For example on page 1, the immunological effects of gene transfer are disclosed. These effects only occur *in vivo*, because there is no functioning immune system *in vitro*. Numerous additional references to therapeutic gene and treatment of disease also establish the *in vivo* nature of the method.

Page 3, 3rd paragraph discloses the stability of Adenovirus vectors in the blood and their being highly efficient gene transfer, both *in vitro* and *in vivo*.

Neither the amendment nor the declaration discussed below is believed to add new matter.

The rejections and objection are addressed in the same sequence they appear in the office action.

Specification

Attached is a markup of the figure legends, wherein the parentheses are filled in the description of Figure 3. Withdrawal of the rejection is requested.

Drawings

Applicants have removed G rman text from the figures. Withdrawal of the rejection is requested.

Anticipation

Preliminary Remarks

Examiner is respectfully reminded that it is well established prosecution practice that a proper reference under 35 USC §§102 or 103 must be enabling in the sense of 35 USC §112, ¶1, but neither Nabel nor Mudryj is enabling to that extent. Pertinent is the following quote from *In re Le Grice*, 133 USPQ 365, 374 (CCPA 1962):

"[T]he proper test of a description in a publication as a bar to a patent as the clause is used in section 102(b) requires a determination of whether one skilled in the art to which the invention pertains *could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention* on which a patent is sought. [Emphasis added.]"

See also, *In re Hoeksema*, 158 USPQ 596, 601 (CCPA 1968), wherein the Court stated:

> "While *In re Le Grice* was bottomed on an issue arising under 35 U.S.C. 102 where the reference was a 'printed publication,' that test, in our view, is also properly applicable to issues arising under 35 U.S.C. 103."

In sum, the mere disclosure of an embodiment of a method, without teaching how to achieve the method does not rise to an enabling disclosure. The "test" for whether or not a reference does provide an enabling disclosure is establishing that the prior art reference teaches all sources and methodology in such detail that a person of ordinary skill in the art could reproduce the results reported therein. Clearly, neither Nabel nor Murdryj is adequate to satisfy this test. Consequently, the anticipation rejections should be withdrawn.

Murdryj

Murdryj explicitly demonstrates the opposite of Applicants' results. Co-expressing a construct with the p21 construct reduces expression. Col. 10, Ex. 12. She further describes that the p21 construct was reported of inhibiting other genes.

It is not clear why Murdryj obtains an opposite effect, but it must be a direct result of some aspect of the methodology disclosed in the reference, or what she was assaying. In all, it is not logical that a method that clearly demonstrates the opposite effect can enable the claimed method. Accordingly, Murdryj cannot anticipate the claims.

Therefore, the rejection should be withdrawn.

Nabel

Murdryj indicates that it is not a given that merely expressing p21 with another gene will provide increased expression of the second gene. Thus, when considering the Nabel reference that does not even disclose, exemplify or teach coexpression of a second gene with p21, this reference cannot reasonably be found to be enabling.

Examiner asserts that Nabel teaches a method of transferring an expressible p21 construct and an additional expressible construct into a target cell. Examiner also asserts that Nabel has achieved the results *in vivo*. In support Examiner cites various text in the reference.

1. Pages 3-6. These pages provide no discussion or evidence to indicate that p21 was co-expressed with any gene. This cannot reasonably be viewed as anticipatory subject matter. In addition, as described above, there is certainly nothing that approximates an enabling disclosure.

2. Page 11-12. Again, there is no disclosure for coexpressing gene(s) with p21, and certainly no disclosure that doing so would result in an increase of the coexpressed gene. On lines 19-27, there is a brief mention of "g netic therap utics" followed in parenthesis by the term HLA-B7 which is a protein, a

memb r of the histocompatibility antig n family. It appears that Nab l is discussing the use of recombinantly produced peptides. There is not one reference on pages 11-12 that describe coexpression of p21 and a second gene as a method of maintaining the second gene's expression.

3. Claim 10, merely claims a method without any exemplified embodiment or guidance in accomplishing his method. There is no guidance in performing such a method, neither is there an indication that applicants' claimed method of increasing the expression level of a second gene can be attained.

Claim 10 merely mentions coexpressing p21 with a vector encoding various therapeutic agents. However, he does not teach coexpression, which as required of an anticipatory reference. This mere disclosure does not constitute enabling disclosure when the entire reference is taken as a whole.

Applicants respectfully remind the Examiner that if the Examiner is relying on a theory of inherency as to the overall result achieved by the reference's methods, then the intrinsic and extrinsic evidence must make clear that such element or result is *necessarily* present in the thing described in the reference. *In re Robertson,* 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). This has not been achieved in the present rejection.

In fact, the indisputable fact that Murdyj's methods do not lead to the enhanced expression of the second coexpressed gene, precludes a forceful argument supporting the rejection based on inherency. If anything, Murdryj discloses a different method.

On this basis, the Examiner should withdraw the rejection.

§ 112 - Enablement

First, the rejection as stated is founded on prior art that does not appear to teach material relevant to the claimed method. It is noted that the present claims and specification do not disclose overexpression of p21 or any other genes. The potential

and undefined toxicity of gene ov rexpression cannot play a role in this rejection unless Examiner can demonstrate within Applicants' data or specification evidence that such overexpression is demonstrated, explicitly or inherently.

Applicants would remind the Examiner that the specification must be accepted as true in the absence of reasonable doubts supported by sound technical reasoning or evidence. *In re Marzocchi et al.*, 169 USPQ 367, 369 (CCPA 1971). Absent such data or other basis for reasoning along similar lines, the rejection based on the assumption that the claimed subject matter encompasses overexpression is improper and should be withdrawn.

It is respectfully emphasized that the method is directed to increasing the expression of a coexpressed gene when compared to the gene's expression when not coexpressed with p21. This was not explored in Kondo or Kokunai. There is no discussion of the effects of p21 on the coexpression of a second gene. Respectfully, how can Examiner draw any conclusions from these citations that are relevant to the claims.

In addition, it is not even clear that Kokunai and Kondo have shown different results. Kokunai shows cell cycle arrest, while Kondo shows inhibition of DNA synthesis. This is the same result. When DNA synthesis, i.e., S phase of cell cycle, is arrested then the entire cell cycle is arrested. Where is the contradiction?

If Examiner is suggesting that cessation of cell cycle is the prelude to apoptosis, it is respectfully pointed out that many, if not most cell types in a mammal are in cell cycle arrest – adult hepatocytes, neurons, lymphocytes [unless challenged with antigen], spermatocytes and oocytes, adult muscle cells and adipocytes are just a partial list. If all of these cell types became apoptotic based on there cell cycle arrest, an organism could not survive.

Last, it is pointed out that simply because Applicants demonstrate that inhibiting apoptosis is often correlated with their demonstrated increased coexpression, it may be only one explanation for the effect of p21 on a coexpressed gene. In other words, it is not a necessary condition to the claimed method.

Rule 132 Declaration

Applicants have submitted a Rule 132 declaration demonstrating that their method is functional far beyond LoVo cells. Primary, normal (i.e., non-tumorigenic) hepatocyes also demonstrate the expected effect of p21 on coexpression.

The enhanced coexpression also is demonstrated by genes encoding evolutionarily divergent proteins -- bacterial β-galactosidase and human α-1-antitrypsin. These experiments indicate that persons in the art would expect that coexpressing virtually any protein encoding gene would show the same enhanced effect.

The data in the declaration also demonstrate that the method works *in vivo*. Given the fact that Adenoviral vectors affect many cell types, it is clear that the in vivo effect is consistent with the expectation that the claimed method will induce coexpression in many different cell types.

Thus, the rejection based on the alleged lack of enablement should be withdrawn. The specification provides ample guidance to perform the method with any cell type. In addition, the specification provides for assays used to definitively determine the extent to which the method works. Therefore, it is believed that the method is enabled to full extent of the claims. It would not require undue experimentation to practice the claims. It may require a large quantity of work, but this is not sufficient for maintaining an enablement rejection.

Neither is possibility that some cell types may not show the effect, sufficient to maintain the rejection. The demonstration of inoperative embodiments is not fatal in the nonenablement sense. However, there have been no inoperable embodiments using the Applicants' methodology.

Withdrawal of the rejection is respectfully requested.

Written Description

Examiner seems to be suggesting that persons in the art would not be aware from the description that the claimed method was in possession of the Applicants, because tissue culture cells and/or primary cells were not specifically mentioned.

Persons of skill in the art would readily appreciate from the specification that the method encompasses cultured cells, primary cells and in vivo. See Rule 132 declaration to support this conclusion. For example on page 1, the immunological effects of gene transfer are disclosed. These effects only occur *in vivo*, because there is no functioning immune system *in vitro*. Numerous additional references to therapeutic gene and treatment of disease also establish the *in vivo* nature of the method. Tissue culture cells have also been used.

The rejection does not take into consideration that it is known in the art that mammalian cells in research will be either in tissue culture lines, primary cultures derived from explants, or *in vivo*. There are no other possibilities, thus, persons in the art would understand thatthe specification encompasses all of these. The Rule 132 declaration extends this conclusion by demonstrating that the method is enabled in these types of cell preparations.

Accordingly, the rejection should be withdrawn.

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Respectfully Submitted,

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